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Comparison of Long-term Outcome after Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting in Patients with Unprotected Left Main Coronary Artery Disease from the CREDO-Kyoto PCI/CABG registry cohort-2

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Running head: PCI versus CABG in Left Main Disease.

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Abstract: Long-term outcome of percutaneous coronary intervention (PCI) compared to coronary artery bypass grafting (CABG) for unprotected left main coronary artery disease (ULMCAD) remain to be investigated. We identified 1005 patients with ULMCAD among 15939 patients with first coronary revascularization enrolled in the CREDO-Kyoto PCI/CABG registry cohort-2. Cumulative 3-year incidence of a composite of death/myocardial infarction (MI)/stroke was significantly higher in the PCI group than in the CABG group (22.7% vs. 14.8%, log rank p=0.0006). However, the adjusted outcome was not different between the PCI and CABG groups (hazard ratio (HR): 1.30, 95% confidence interval (C.I): 0.79-2.15, p=0.30). The stratified analysis using the SYNTAX score demonstrated that risk for a composite of death/MI/stroke was not different between the 2 treatment groups in patients with low (<23) and intermediate SYNTAX score (23-33) (adjusted HR 1.70, 95% CI: 0.77-3.76, p=0.19 and adjusted HR 0.86, 95% CI: 0.37-1.99, p=0.72, respectively), while in patients with high SYNTAX score (≥ 33), it was significantly higher after PCI than after CABG (adjusted HR 2.61, 95% CI: 1.32-5.16, p=0.006). In conclusions, the risk of PCI for serious adverse events seemed to be comparable to that after CABG in ULMCAD patients with low or intermediate SYNTAX score, while PCI as compared with CABG was associated with a higher risk for serious adverse events in patients with high SYNTAX score.

Key words: coronary artery disease, stents, coronary artery bypass grafting, prognosis

Text

In recent years, several observational studies reported favorable clinical outcomes of percutaneous coronary intervention (PCI) using drug eluting stent (DES) in patients with unprotected left main coronary artery disease (ULMCAD) [1-3]. SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) randomized trial reported comparable safety and efficacy outcomes of PCI relative to coronary artery bypass grafting (CABG) in the left main disease subset[4-6]. Reflecting these study results, updated clinical guidelines for ULMCAD regarded PCI as an alternative to CABG in patients with less complex coronary anatomy or in patients with high surgical risk[7, 8]. However, number of patients enrolled in these trials was still insufficient in drawing definitive conclusions on the role of PCI in treating patients with ULMCAD. Therefore, we evaluated the long-term clinical outcome of PCI relative to CABG and the utility of the SYNTAX score for risk stratification in patients with ULMCAD in a large observational database in Japan.

Methods

The CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome Study in Kyoto) PCI/CABG registry cohort-2 is a physician-initiated, non-company sponsored, multi-center registry that enrolled consecutive patients undergoing first coronary revascularization among 26 centers in Japan between January 2005 and December 2007. The

relevant ethics committees in all 26 participating centers (Supplemental Appendix A) approved the research protocol. Because of retrospective enrollment, written informed consents from the patients were waived. However, patients who refused participation in the study when contacted for follow-up were excluded.

The study design and patient enrollment in the registry have been described in detail previously[9]. Among 15939 patients enrolled in the registry, the study population for the current pre-specified sub-analysis of the CREDO-Kyoto PCI/CABG registry cohort-2 consisted of 1005 patients with ULMCAD (PCI: 365 patients, and CABG: 640 patients), excluding those patients with refusal for study participation, concomitant non-coronary surgery and acute myocardial infarction (Figure 1).

Demographic, angiographic, and procedural data were collected from hospital charts according to pre-specified definitions by experienced research coordinators in the independent research organization (Research Institute for Production Development, Kyoto, Japan) (Supplemental Appendix B). Patients with ULMCAD were identified using the angiographic information recorded in their hospital charts. Therefore, the current study population included those patients in whom PCI was not attempted for the left main coronary artery lesions based on clinical judgments. The definitions for clinical characteristics are described in the Supplemental Text.

The SYNTAX score was calculated using the SYNTAX score calculator (available at http://www.syntaxscore.com) by a dedicated SYNTAX score committee (Supplemental Appendix C) in a blinded fashion to the clinical data. Intra- and inter-observer variabilities of the SYNTAX score calculation in our group were previously reported[10]. The cutoff values for the SYNTAX score tertiles (low-score: <23, intermediate-score: 23-33, and high-score: ≥33) were defined according to the analysis in the SYNTAX trial[4, 5].

The primary outcome measure for the current analysis was defined as a composite of all-cause death, myocardial infarction (MI), and stroke. Other pre-specified endpoints included all-cause death, cardiac death, MI, stroke, and coronary revascularization. Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Any death during the index hospitalization for coronary revascularization was regarded as cardiac death. MI was defined according to the definition in the Arterial Revascularization Therapy Study[11]. Stroke was defined as ischemic or hemorrhagic stroke requiring hospitalization with symptoms lasting >24 hours. Coronary revascularization was defined as either PCI or CABG for any reasons. Scheduled staged coronary revascularization procedures performed within 3 months of the initial procedure were not regarded as follow-up events, but were included in the index procedure.

Collection of follow-up information was mainly conducted through review of inpatient and outpatient hospital charts by the clinical research coordinators in the independent research organization. Additional follow-up information was collected through contact with patients, relatives and/or referring physicians by sending mail with questions regarding vital status, additional hospitalizations, and status of antiplatelet therapy. Death, MI, stent thrombosis (ST), and stroke were adjudicated by the clinical event committee (Supplemental Appendix D).

Since final data collection for follow-up events was initiated on July 1st, 2009, follow-up events were censored on this date. Median follow-up duration for surviving patients was 1027 (inter-quartile range [IQR]: 734-1311) days. Complete 1-year follow-up information was obtained in 95.4% of patients (96.4% in the PCI group and 94.8% in the CABG group: p=0.24).

Categorical variables were presented as number and percentage and were compared with the chi-square test. Continuous variables were expressed as mean value ± standard deviation (SD) or median with Interquartile range (IQR). Continuous variables were compared using the Student's t-test or Wilcoxon rank sum test based on their distributions.

Cumulative incidence was estimated by the Kaplan-Meier method and differences were assessed using the log-rank test. The effects of PCI relative to CABG for individual endpoints were expressed as hazard ratios (HR) with 95% confidence intervals (CI). In the entire study

population, HR was estimated using the non-parsimonious multivariable Cox proportional hazard models adjusted for the 30 clinically relevant factors in Table 1, which was consistent with previous reports from the current registry. Continuous variables were dichotomized using clinically meaningful reference values or median values. Proportional hazard assumptions for potential independent risk-adjusting variables were assessed on log (time) versus log [-log (survival)] plots stratified by the variable, and the assumptions were verified as acceptable for all variables. We incorporated the 26 participating centers in the Cox proportional hazard models as the stratification variable.

The unadjusted and adjusted risks of PCI relative to CABG for the primary outcome measure were evaluated in each SYNTAX score category as a subgroup analysis to assess utility of the SYNTAX score for risk stratification. In addition to the modes of coronary revascularization (PCI versus CABG), 4 variables with p value <0.05 in the previously described full model (Age >= 75 years, Estimated glomerular filtration rate <30 mL/min/1.73m^2, without hemodialysis, Hemodialysis, and Proton pump inhibitors) were included in the multivariable models for the subgroup analysis reflecting our preference for parsimonious models to avoid over-fitting.

Statistical analyses were conducted by a physician (Shiomi H) and a statistician (Morimoto T) using the JMP 8.0 (SAS Institute Inc, Cary, NC) software and SAS 9.2 (SAS

Institute Inc, Cary, NC) statistical analysis software. All the statistical analyses were two-tailed and p values <0.05 were considered statistically significant.

Results

Patients in the PCI group were older, and more often had malignancy and severe mitral regurgitation, while patients in the CABG group more often had diabetes on insulin therapy, and thrombocytopenia (Table 1).

The CABG group included more patients with complex coronary anatomy and greater numbers of target lesions or anastomoses (Table 1). The SYNTAX scores were available in 932 patients (92.7%). The median SYNTAX score was significantly greater in the CABG group than in the PCI group. Stents were used in 98% of the patients in the PCI group, and at least one DES was used in 78% of the patients. In the PCI group, PCI targeting for ULMCA lesion was performed in 306 patients (83.4%), in whom left main distal bifurcation was involved in 210 patients (68.6%) and DES was used for the left main lesion in 209 patients (68.3%). At least one internal thoracic artery was used in 98.3% of patients in the CABG group, and the prevalence of off-pump CABG was high (64.7%). Baseline medications were significantly different in several aspects between the two groups (Table 1).

The cumulative 3-year incidence of the primary outcome measure (death/MI/stroke) in the PCI group was significantly higher than that in the CABG group (22.7% vs. 14.8%, log

rank p=0.0006) (Figure 2A). However, after adjusting for potential confounders, the risk of PCI relative to CABG for the primary outcome measure was not significantly different (adjusted HR: 1.30, 95% C.I: 0.79-2.15, p=0.30) (Table 2). Regarding survival outcome, the cumulative 3-year incidence of all-cause death and cardiac death were higher in the PCI group than that in the CABG group (13.6% vs. 9.2%, log rank p=0.01, and 7.4% vs. 3.7%, log rank p=0.005, respectively) (Figure 2B, and 2C). However, the adjusted risk for all-cause death and cardiac death were not different between the 2 groups (adjusted HR: 0.79, 95% C.I: 0.40-1.57, p=0.50, and adjusted HR: 1.80, 95% C.I: 0.64-5.09, p=0.27, respectively) (Table 2). The cumulative 3-year incidence of MI was significantly higher in the PCI group compared to the CABG group (5.5% vs. 2.3%, log rank p=0.003) (Figure 2D). However, the adjusted risk of PCI relative to CABG for MI was not significantly different (adjusted HR: 2.47, 95% C.I: 0.81-7.54, p=0.11), although the point estimate strongly favored CABG (Table 2). The cumulative 3-year incidence of definite ST in the PCI group was low (1.5%). The risk for stroke was not different between the two groups (6.6% vs. 5.5%, log rank p=0.43, adjusted HR: 0.79, 95% C.I: 0.30-2.08, p=0.63) (Figure 2E, and Table 2). PCI was associated with a markedly higher risk for any coronary revascularization compared to CABG (43.4% vs. 11.2%, log rank p<0.0001, adjusted HR: 5.83, 95% C.I: 3.74-9.09, p<0.0001) (Figure 2F, and Table 2).

Clinical outcome was compared between the PCI and CABG groups among the 3 categories of coronary anatomic complexities stratified by the SYNTAX score. The cumulative 3-year incidences of the primary outcome measure were not different between the PCI and CABG groups in patients with low and intermediate SYNTAX score (22.8% vs. 14.7%, log rank p=0.08, and 19.5% vs. 14.3%, log rank p=0.21). However, the cumulative 3-year incidence of the primary outcome measure was markedly higher in the PCI group than that in the CABG group in patients with high SYNTAX score (27.4% vs. 16.8%, log rank p=0.006) (Figure 3). After adjustment for potential confounders, the risk of PCI relative to CABG for the primary outcome measure remained significantly higher in patients with high SYNTAX score (adjusted HR: 2.61, 95% C.I: 1.32-5.16, p=0.006), while it was not significantly different in patients with low and intermediate SYNTAX score (adjusted HR: 1.70, 95% C.I: 0.77-3.76, p=0.19, and adjusted HR: 0.86, 95% C.I: 0.37-1.99, p=0.72).

Discussion

The main findings in the current study were as follows; (1) the 3-year clinical outcome of PCI was comparable with that of CABG in terms of serious cardiovascular events in patients with ULMCAD; (2) the risk for serious cardiovascular events was not significantly different between PCI and CABG in patients with low or intermediate SYNTAX score, while it was markedly higher after PCI as compared with CABG in patients with high SYNTAX score.

The favorable outcome of PCI for the treatment of ULMCAD as demonstrated in the left main subset of the SYNTAX trial, led to the recently updated recommendation of PCI for ULMCAD[1-6]. However, evidence from randomized trials comparing PCI using DES with CABG in patients with ULMCAD is quite limited. Indeed, Boudriot et al. failed to demonstrate non-inferiority of PCI using SES relative to CABG with respect to major adverse cardiac events in patients with ULMCAD in their randomized trial, while Park et al. showed non-inferiority of PCI relative to CABG with respect to MACCE in the PRECOMBAT Trial[12, 13]. Moreover, the results from randomized trials should be interpreted cautiously for application to daily clinical practice because selected patients with relatively low risk profiles were generally enrolled in the randomized trials. Therefore, the results from large-scale observational studies are also important. The current analysis from a multicenter registry in Japan suggested comparable long-term clinical outcome in terms of a composite of death/MI/stroke between PCI and CABG in patients with ULMCAD, which is consistent with previous observational studies as well as SYNTAX and PRECOMBAT randomized trials[1, 4-6, 13, 14].

The appropriate selection of patients with ULMCAD for PCI is the most important consideration while expanding the use of PCI for ULMCAD. Risk stratification using the SYNTAX score has drawn attention for the selection of revascularization procedures in complex coronary artery disease, such as ULMCAD or triple vessel coronary artery disease[4].

However, the utility of the SYNTAX score for risk stratification in ULMCAD is still controversial[15-17]. Capodanno et al. reported that PCI was associated with a higher mortality than CABG in ULMCAD patients with SYNTAX score >= 34 in 2 Italian centers[15]. In contrast, Kim et al. reported the SYNTAX score failed to stratify clinical outcome in patients with ULMCAD in a subanalysis of the MAIN-COMPARE study, although they demonstrated the utility of the SYNTAX score for risk stratification in patients who received DES[16, 17]. The current study provided additional support for the utility of the SYNTAX score for risk stratification in patients with ULMCAD. The results stratified by the SYNTAX tertiles in the current study were consistent with the results of the SYNTAX randomized trial[5]. Therefore, PCI for ULMCAD patients with high SYNTAX score should be discouraged unless the operative risk is prohibitively high. On the other hand, the long-term clinical outcome of PCI seemed to be comparable to that of CABG in patients with low or intermediate SYNTAX score, supporting recent trend for expanding use of PCI in this category of ULMCAD patients. However, the number of patients studied was still insufficient to advocate widespread use of PCI in ULMCAD patients with less complex coronary anatomy. The results of the EXCEL trial, which is an ongoing randomized trial comparing PCI using everolimus-eluting stents with CABG in 2600 ULMCAD patients with SYNTAX score <33, would provide further guidance for PCI use in this important subset of patients.

There are several important limitations in this study. First and most importantly, observational study design precluded definitive conclusions in terms of superiority of either PCI or CABG due to selection bias and unmeasured confounders. Since CABG had been considered to be the gold standard for ULMCAD patients, selection bias could be greater in patients with ULMCAD as compared with other subsets of severe coronary artery disease such as triple vessel coronary artery disease. Therefore, the results in the current study should be interpreted very carefully. Furthermore, the results from the SYNTAX subgroup analyses should be regarded as hypothesis generating. Second, number of patients enrolled was still small and SYNTAX score data were not available for all patients. Third, the duration of follow-up might not be sufficient to evaluate long-term outcome of coronary revascularization. Finally, we did not exclude those patients in whom PCI was not attempted for the left main coronary artery lesions based on clinical judgments. The current study population might include patients with less severe left main coronary artery lesions in both PCI and CABG groups.

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Conflict of Interest Disclosures: None of the authors have conflict of interest to disclose.

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Figure Legends

Figure 1. Study flow-chart.

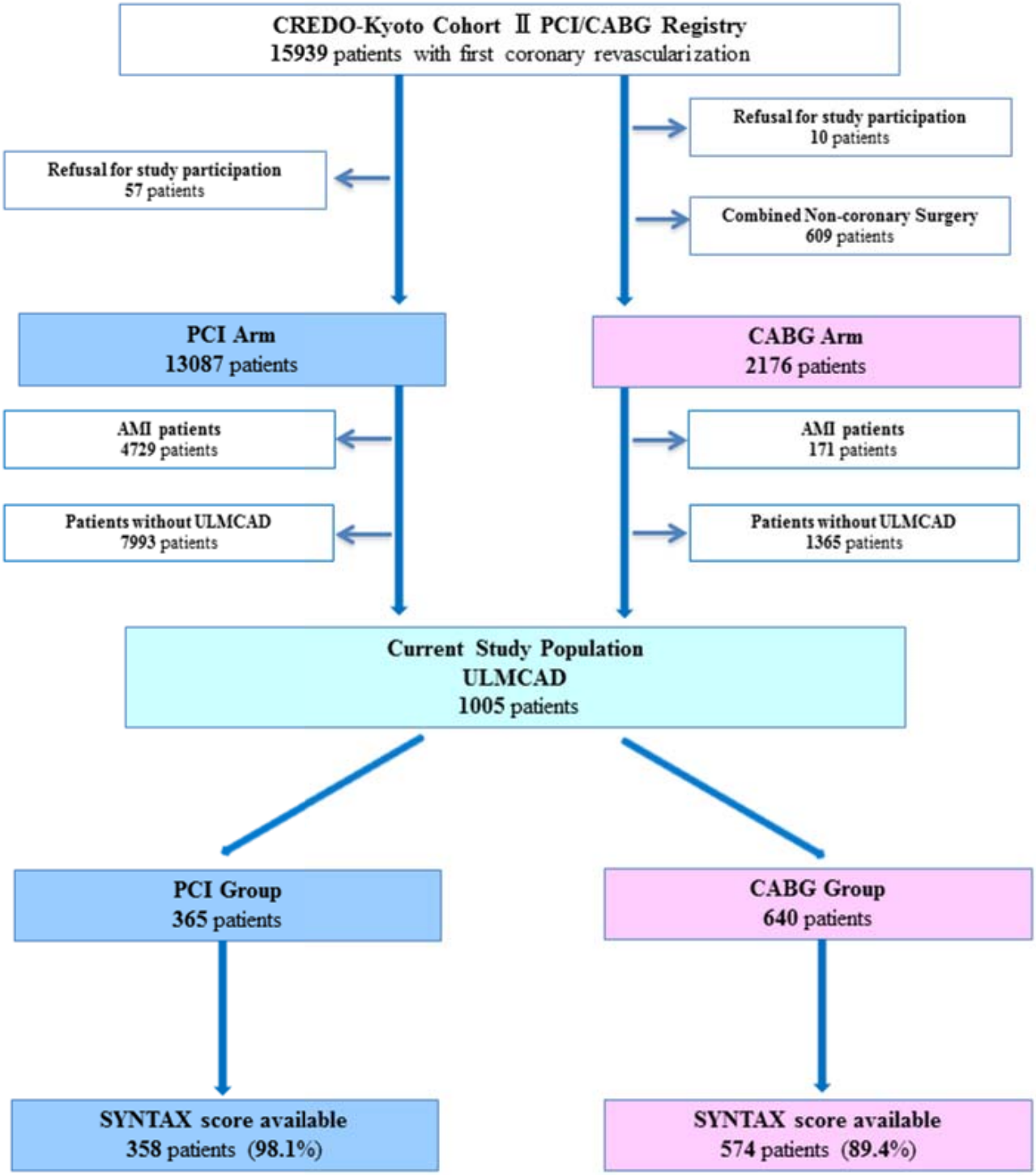
AMI=acute myocardial infarction, CABG=coronary artery bypass grafting, CREDO-Kyoto=Coronary REvascularization Demonstrating Outcome study in Kyoto, PCI=percutaneous coronary intervention, SYNTAX=SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery, and ULMCA=unprotected left main coronary artery.

Figure 2. Kaplan-Meier event curves: PCI versus CABG for A) a composite of all-cause death, myocardial infarction and stroke, (B) all-cause death, (C) cardiac death, (D) stroke, (E) myocardial infarction, and (F) any revascularization.

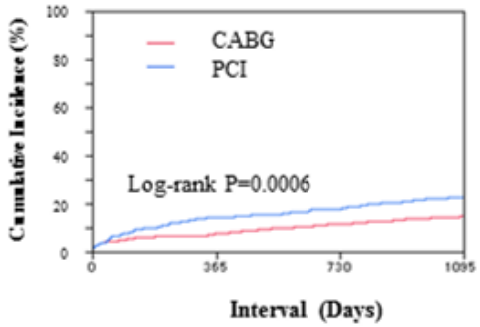
CABG=coronary artery bypass grafting, and PCI=percutaneous coronary intervention.

Figure 3. Kaplan-Meier event curves comparing PCI with CABG for a composite of all-cause death, myocardial infarction and stroke stratified by SYNTAX score tertiles; (A) low SYNTAX score category (<23), (B) intermediate SYNTAX score category (23-33), and (C) high SYNTAX score category (≥33).

CABG=coronary artery bypass grafting, MI=myocardial infarction, PCI=percutaneous coronary intervention, and SYNTAX=SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.

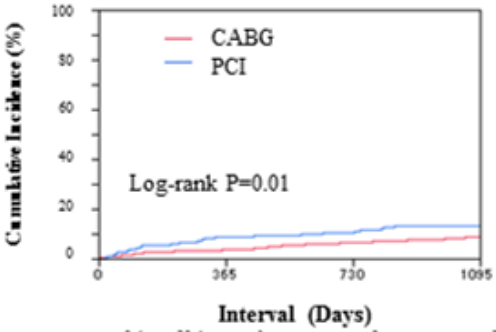


(A) Death/MI/Stroke



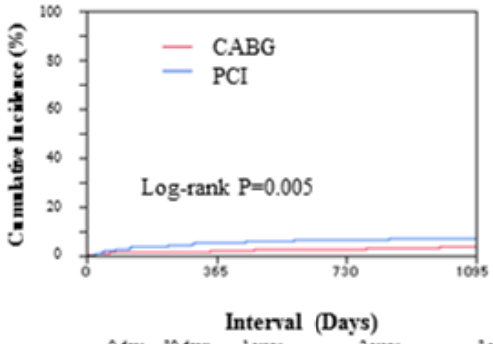
Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		25	48	71	84
N of patients at risk	640	605	561	438	270
Incidence		3.9%	7.7%	11.6%	14.8%
PCI group					
N of events		14	51	63	74
N of pts at risk	365	349	300	228	114
Incidence		3.9%	14.2%	17.9%	22.7%

(B) All-cause Death



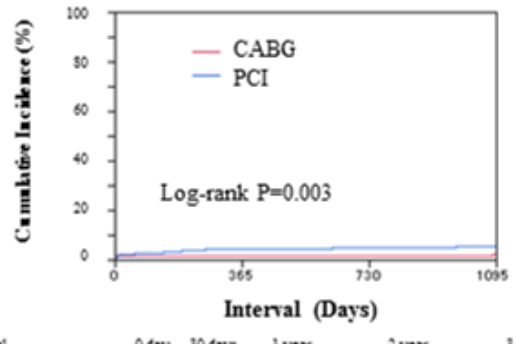
Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		7	23	39	50
N of patients at risk	640	623	585	463	291
Incidence		1.1%	3.7%	6.4%	9.2%
PCI group					
N of events		4	31	38	45
N of pts at risk	365	359	322	248	125
Incidence		1.1%	8.7%	10.8%	13.6%

(C) Cardiac Death



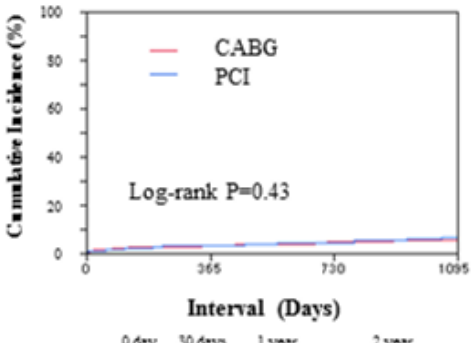
Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		7	14	17	21
N of patients at risk	640	623	585	463	291
Incidence		1.1%	2.3%	2.8%	3.7%
PCI group					
N of events		4	20	24	25
N of pts at risk	365	359	322	248	125
Incidence		1.1%	5.7%	6.9%	7.4%

(D) Myocardial Infarction



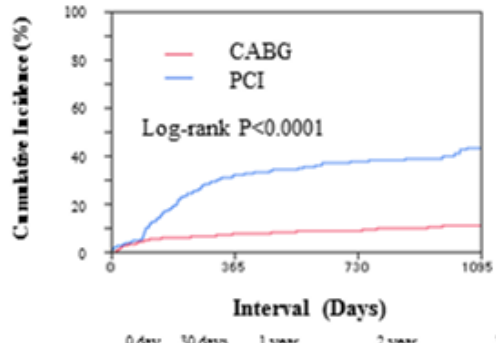
Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		9	10	12	13
N of patients at risk	640	615	576	454	284
Incidence		1.4%	1.6%	1.9%	2.3%
PCI group					
N of events		8	16	17	18
N of pts at risk	365	351	306	234	120
Incidence		2.2%	4.6%	4.9%	5.5%

(E) Stroke



Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		10	20	28	31
N of patients at risk	640	613	568	445	276
Incidence		1.6%	3.2%	4.8%	5.5%
PCI group					
N of events		4	11	15	19
N of pts at risk	365	356	313	240	119
Incidence		1.1%	3.1%	4.4%	6.6%

(F) Any Coronary Revascularization

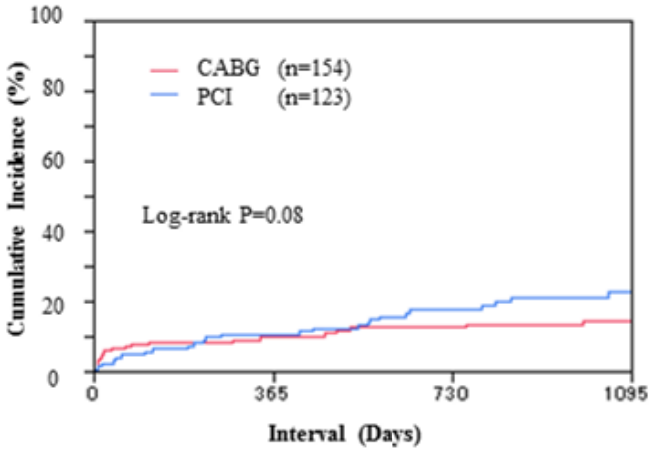


Interval	0 day	30 days	1 year	2 year	3 year
CABG group					
N of events		14	46	55	63
N of patients at risk	640	609	541	422	258
Incidence		2.2%	7.5%	9.1%	11.2%
PCI group					
N of events		12	108	125	133
N of pts at risk	365	347	215	149	63
Incidence		3.3%	32.0%	37.8%	43.4%

Death/MI/Stroke

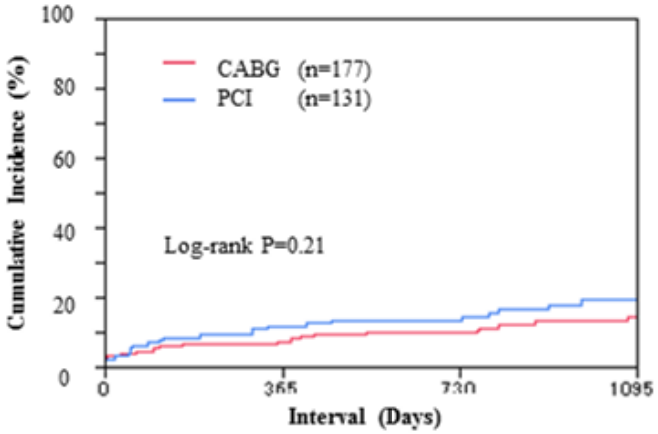
Cumulative 3-Year Event Rates

(A) Low SYNTAX Score (< 23)



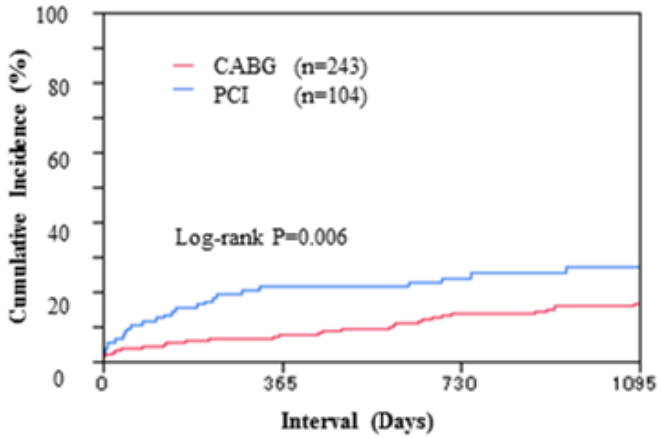
	PCI	CABG	P value
Death/MI/Stroke	25 (22.8%)	21 (14.7%)	0.08
Death	16 (14.3%)	12 (8.8%)	0.19
Cardiac death	8 (7.2%)	7 (4.6%)	0.51
MI	4 (3.4%)	1 (0.7%)	0.03
Stroke	8 (8.6%)	9 (6.0%)	0.42
Coronary revascularization	42 (36.6%)	15 (11.4%)	<0.0001

(B) Intermediate SYNTAX Score (23-33)



	PCI	CABG	P value
Death/MI/Stroke	22 (19.5%)	22 (14.3%)	0.21
Death	14 (12.1%)	15 (10.8%)	0.38
Cardiac death	7 (5.6%)	6 (4.1%)	0.23
MI	4 (4.1%)	3 (1.7%)	0.22
Stroke	6 (5.4%)	7 (4.3%)	0.92
Coronary revascularization	33 (31.5%)	17 (11.4%)	<0.0001

(C) High SYNTAX Score (≥ 33)



	PCI	CABG	P value
Death/MI/Stroke	26 (27.4%)	36 (16.8%)	0.006
Death	14 (14.6%)	19 (8.5%)	0.06
Cardiac death	10 (10.2%)	5 (2.1%)	0.001
MI	10 (10.4%)	7 (3.4%)	0.01
Stroke	5 (6.2%)	15 (7.4%)	0.95
Coronary revascularization	55 (67.4%)	25 (11.5%)	<0.0001

Tables

Table 1: Comparison of Baseline Characteristics Between Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG) Groups

	PCI (n=365)	CABG (n=640)	p value
(A) Clinical characteristics			
Age (years)	71.4±10.1	69.4±9.2	0.001
Age >= 75 years*†	151 (41%)	208 (33%)	0.005
Male*	259 (71%)	490 (77%)	0.051
Body mass index (kg/m^2)	23.4±3.4	23.2±3.0	0.35
Body mass index < 25.0 kg/m^2*	271 (74%)	467 (73%)	0.66
Unstable angina pectoris	52 (14%)	71 (11%)	0.15
Hypertension*	313 (86%)	542 (85%)	0.65
Diabetes mellitus*	155 (42%)	291 (45%)	0.36
on insulin therapy	35 (9.6%)	93 (15%)	0.02
Current smoker*	79 (22%)	157 (25%)	0.30
Heart failure*	76 (21%)	131 (20%)	0.89
Ejection fraction (%)	59.3±14.7	60.2±13.4	0.34
Ejection fraction <= 40%	34 (12%)	56 (9.5%)	0.30
Mitral regurgitation grade 3/4 *	25 (6.9%)	17 (2.7%)	0.002
Prior myocardial infarction*	70 (19%)	105 (16%)	0.27
Prior Stroke (symptomatic)*	54 (15%)	75 (12%)	0.16
Peripheral vascular disease*	45 (12%)	76 (12%)	0.83
Estimated glomerular filtration rate (mL/min/1.73m^2)	62.2 (45.7-74.5)	61.0 (46.6-72.1)	0.20
Estimated glomerular filtration rate <30 mL/min/1.73m^2,without hemodialysis*†	19 (5.2%)	38 (5.9%)	0.63
Hemodialysis*†	26 (7.1%)	44 (6.9%)	0.88
Anemia (Hb <11.0g/dl)*	72 (20%)	128 (20%)	0.92
Platelet count <100 × 10^9/L*	3 (0.8%)	19 (3.0%)	0.02

Chronic obstructive pulmonary disease *	12 (3.3%)	17 (2.7%)	0.57
Liver cirrhosis*	9 (2.5%)	19 (3.0%)	0.64
Malignancy*	58 (16%)	69 (11%)	0.02
(B) Procedural characteristics			
Number of target lesions or anastmoses	2.00±1.03	3.09±1.04	<0.0001
Extent of coronary artery disease			<0.0001
Isolated ULMCA disease	31 (8.5%)	57 (8.9%)	
ULMCA + 1 vessel disease	89 (24.4%)	108 (16.9%)	
ULMCA + 2 vessel disease	132 (36.2%)	182 (28.4%)	
ULMCA + 3 vessel disease	113 (31.0%)	293 (45.8%)	
Target of proximal LAD*	174 (48%)	451 (70%)	<0.0001
Target of Chronic total occlusion*	45 (12%)	166 (26%)	<0.0001
Emergency procedure	34 (9.3%)	50 (7.8%)	0.41
SYNTAX score	26.5 (21-34)	30 (22-40)	<0.0001
Low <23	123 (34.4%)	154 (26.8%)	
Intermediate 23-33	131 (36.6%)	177 (30.8%)	0.0002
High >=33	104 (29.1%)	243 (42.3%)	
Total number of stents	2.78±1.70	—	—
Total stent length (mm)	58.7±41.0	—	—
Stent use	357 (98%)	—	—
Drug-eluting stent use	277 (78%)	—	—
Internal thoracic artery use	—	629 (98%)	—
Off Pump	—	414 (65%)	—
Baseline Medications			
Antiplatelet therapy			
Thienopyridine	362 (99%)	72 (11%)	<0.0001
Ticlopidine	316 (87%)	67 (94%)	0.07
Clopidogrel	46 (13%)	4 (5.6%)	
Aspirin	361 (99%)	632 (99%)	0.83
Cilostazol*	45 (12%)	41 (6.4%)	0.002
Other medications			
Statins*	184 (50%)	199 (31%)	<0.0001

Beta-blockers*	110 (30%)	174 (27%)	0.32
Angiotensin converting enzyme inhibitor /Angiotensin receptor blocker*	191 (52%)	211 (33%)	<0.0001
Nitrates*	170 (47%)	230 (36%)	0.001
Calcium channel blockers*	171 (47%)	332 (52%)	0.13
Nicorandil*	94 (26%)	277 (43%)	<0.0001
Warfarin*	30 (8.2%)	244 (38%)	<0.0001
Proton pump inhibitors*†	92 (25%)	263 (41%)	<0.0001
H2-blockers*	78 (21%)	204 (32%)	0.0003

Continuous variables are shown as mean ± SD or median (Interquartile range).

* Risk adjusting variables selected for Cox proportional hazard models.

† Risk adjusting variables selected for the multivariable models (parsimonious models for the subgroup analysis).

Table 2: Univariate and Multivariate Analysis for 3-Year Clinical Outcomes: Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting

	PCI (n=365) N of events (Incidence)	CABG (n=640) N of events (Incidence)	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
Death/MI/Stroke	74 (22.7%)	84 (14.8%)	1.67 (1.24-2.24)	0.0006	1.30 (0.79-2.15)	0.30
Death	45 (13.6%)	50 (9.2%)	1.61 (1.10-2.34)	0.01	0.79 (0.40-1.57)	0.50
Cardiac death	25 (7.4%)	21 (3.7%)	2.20 (1.26-3.86)	0.005	1.80 (0.64-5.09)	0.27
MI	18 (5.5%)	13 (2.3%)	2.72 (1.38-5.51)	0.003	2.47 (0.81-7.54)	0.11
Stroke	19 (6.6%)	31 (5.5%)	1.25 (0.72-2.12)	0.43	0.79 (0.30-2.08)	0.63
Coronary revascularization	133 (43.4%)	63 (11.2%)	4.43(3.31-5.98)	<0.0001	5.83(3.74-9.09)	<0.0001

SUPPLEMENTAL MATERIAL

Supplemental Text

Definitions for Clinical Characteristics

Baseline clinical characteristics, such as prior myocardial infarction, heart failure, hypertension, current smoking, atrial fibrillation, chronic obstructive lung disease, liver cirrhosis and malignancy were regarded as present when these diagnoses were recorded in the hospital charts. Elderly patients were defined as those patients >=75 years of age. Unstable angina was defined as Braunwald classification type 3. Diabetes was defined as treatment with oral hypoglycemic agents and/or insulin, prior clinical diagnosis of diabetes, glycated hemoglobin level >=6.5%, or blood glucose level >=200 mg/dl. Blood glucose test results in the acute phase of acute myocardial infarction were not used for the diagnosis of diabetes. Prior stroke included both ischemic and hemorrhagic stroke and was defined as stroke with neurological symptoms lasting >24 hours. Peripheral vascular disease was regarded to be present when carotid, aortic, or other peripheral vascular disease was being treated or scheduled for surgical or endovascular interventions. Left ventricular ejection fraction (LVEF) was measured either by contrast left ventriculography or echocardiography. Patients with LVEF <=40% were regarded as having left ventricular dysfunction. Renal function was expressed as estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease (MDRD) formula modified for Japanese patients[1]. Anemia was defined as blood hemoglobin level less than 11.0 g/dl. Thrombocytopenia was defined as platelet count $<100*10^9$/L. A bifurcation lesion was defined as a lesion requiring insertion of a guidewire into the side-branch. Baseline medications were regarded as present if prescribed during the index hospitalization.

Reference

1. Matsuo S, Imai E, Horio M, et al; Collaborators developing the Japanese equation for estimated GFR. Revised equation for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis.* 2009;53:932-935.

Supplemental Appendix A: List of participating centers and investigators for the CREDO-Kyoto AMI Registry

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Masao Imai (Kyoto University Hospital), Kyohei Yamaji (Kokura Memorial Hospital), Kazuya Nagao (Osaka Red Cross Hospital), Shunsuke Funakoshi (Kobe City Medical Center General Hospital), Natsuhiko Ehara (Kobe City Medical Center General Hospital), Koji Hanazawa (Tenri Hospital), Akihiro Tokushige (Kagoshima University Hospital), Tomohisa Tada (Deutsches Herzzentrum), Masahiro Natsuaki (Kyoto University Hospital), Junichi Tazaki (Kyoto University Hospital), Hiroki Shiomi (Kyoto University Hospital), Yoshihiro Kato (Saiseikai Noe Hospital), Mamoru Hayano (Gunma Cardiovascular Center), Syunichiro Niki (Hirakata Kohsai Hospital), Nobuya Higashitani (Kyoto University Hospital), Mitsuhiko Yahata (Kyoto University Hospital), Sayaka Saijo (Hyogo Prefectural Amagasaki Hospital), Yuichi Kawase (Japanese Red Cross Wakayama Medical Center).

Supplemental Appendix D: List of the clinical event committee members

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